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31/4436, A61P 9/00

Adenosine receptor-specific ligand medicaments, comprising new
or known 6-amino-4-phenyl-2-oxy-pyridine-3,5-dicarboxylic
derivatives, useful e.g. for treating cardiovascular diseases, cancer,
inflammation, pain or diabetes (Ger)

C2002-195540 NAE AG AL AM AT AU AZ BA BB BG BR BY BZ
CA CH CN CO CR CU CZ DE DK DM DZ EC EE ES
FI GB GD GE GH GM HR HU IL IN IS JP KE KG
KP KR LZ LC LR LS LT LU LV MA MD MG MK
MN MW MX MZ NO NZ OM PH PL PT RO RU SD
SE SG SI SK SL TJ TM TN TR TT TZ UA UG US UZ
VN YU ZA ZM ZW) R(At BE CH CY DE DK EA ES
FI FR GB GH GM GR IE IT KE LS LU MC MW MZ
NL OA PT SD SE SL SZ TR TZ UG ZM ZW)

Addit. Data: ROSENTRETER U, KRAEMER T, VAUPEL A,
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B(6-H, 7-D4B, 14-C, 14-C3, 14-D2, 14-F1, 14-F2, 14-
F3, 14-F7, 14-H1, 14-J1A3, 14-J1A4, 14-K1, 14-N7, 14-N12, 14-N16,
14-N17, 14-P2, 14-S4) .11

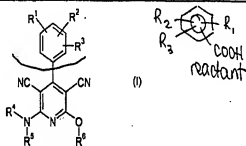
NOVELTY

The use of 6-amino-4-phenyl-2-oxy-pyridine-3,5-dicarboxylic
derivatives (I) for the prophylaxis and/or treatment of diseases is new.
Compounds (I) are new, with some specific exclusions.

DETAILED DESCRIPTION

Pyridine derivatives of formula (I) and their salts, hydrates,
hydrated salts and solvates are claimed for the prophylaxis and/or
treatment of diseases.

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R₁ - R₃ = alkyl (optionally substituted (os) by 1-3 of OH, OT,
cycloalkyl, alkenyl, alkynyl, halo or aryloxy); aryl (os by 1-3
of halo, NO₂, OT, COOH, COOT, NHT or NT₁); alkoxy
(os by 1-3 of OH, OT, 3-6C cycloalkyl, alkenyl, alkynyl,
aryl, Het, aryloxy, halo, CN, COOT, NH₂, NHT or NT₂); or
H, OH, halo, NO₂, CN or -NHCOR₁;

or R₁ + R₂ (on adjacent C) = group completing a 5-7 membered
saturated or partially unsaturated
heterocycle containing 1 or 2 of N, O
and/or S as heteroatom(s) (os by Tor
=O);

T = 1-4C alkyl;

Het = 5-10 membered heteroaryl containing 1-3 of N, O and/or S as
heteroatom(s);

R₂ = alkyl (os by OH or OT), cycloalkyl or aryl (os as in R₁);

R₄, R₅ = H, alkyl (os by OH, OT, cycloalkyl, aryl or Het¹) or 3-BC
cycloalkyl (os by OH or alkyl);

or NR₁R₅ = 5-7 membered saturated or partially unsaturated
heterocycle (optionally containing 1 or 2 of N, O and/or S
as further heteroatom(s) and os by 1-3 of =O, F, Cl, OH,
1-6C alkyl or 1-6C alkoxy);

Het¹ = 5- or 6-membered heteroaryl containing 1-3 of N, O and/or S as
heteroatom(s);

R₆ = cycloalkyl or alkyl (os by cycloalkyl, OH, OT, alkenyl, alkynyl,
aryl or Het, aryl and Het themselves being os by halo, T, OT,
NH₂, NHT, NT₁, NO₂, CN or OH);

unless specified otherwise alkyl moieties have 1-8C, alkenyl or alkynyl
moieties 2-4C, cycloalkyl moieties 3-7C and aryl moieties 6-10C.

INDEPENDENT CLAIMS are included for:

(i) (I) (including salts etc.) as new compounds, with the exception of (I);
R₁ - R₃ = H; R₄ = Me, Et, propyl or isopropyl); (I); R₁ = 4-Me, 4-
OMe, 2-Cl, 4-Cl, 3-Me or 2-OH; R₂ - R₃ = H; R₄ = Et; (I); R₁ = 4-F

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or 4-OMe; R₂ - R₃ = H; R₄ = Me) or (I); R₁ + R₂ = OCH₂O; R₃ - R₄
= H; R₅ = Me); and
(ii) the preparation of the new compounds (I).

ACTION

Cardiac; vasotropic; hypotensive; antiarteriosclerotic;
antidysrhythmic; thrombolytic; anticoagulant; cerebroprotective; uterine;
cytostatic; antiinflammatory; antidiabetic; dermatological;
neuroprotective; neurotic; antiparkinsonian; analgesic; hepatoprotective;
antidiabetic; vulnary.

MECHANISM OF ACTION

Adenosine receptor-specific ligand. (I) are in general selective
ligands for adenosine-A₁, -A₂ and/or -A_{2b} receptors; in particular (I);
R₁ + R₂ = OCH₂O, OCH₂CH₂O or O(CH₂)₂O are selective for A₁
receptors and (I); one of R₁ - R₃ = NHCOR₁; one of R₄ and R₅ =
benzyl or pyridylmethyl) are selective for A₁ and/or A_{2b} receptors.
The ligands may be agonists or antagonists.

USE

(I) are especially used for the treatment and/or prophylaxis of
cardiovascular diseases, urogenital diseases, cancer, inflammatory or
neuroinflammatory diseases, pain, respiratory tract diseases, liver
fibrosis, liver cirrhosis or diabetes (all claimed). Specific disorders to
be controlled include coronary heart disease, hypertension, restenosis,
arteriosclerosis, tachycardia, arrhythmia, stable or unstable angina
pectoris, atrial flutter, thromboembolic disease, myocardial infarction,
cerebral stroke, transitory ischemic attacks, bladder incontinence, erectile
dysfunction, female sexual dysfunction, asthma, inflammatory
dermatitis, Alzheimer's disease, Parkinson's disease, chronic
bronchitis, pulmonary emphysema, bronchiectasis, cystic fibrosis,
pulmonary hypertension, diabetes mellitus or wound healing
deficiency.

ADVANTAGE

(I) have higher selectivity for particular adenosine receptor
subtypes than prior art compounds

SPECIFIC COMPOUNDS

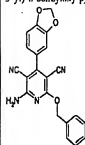
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(CON 4)

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20 Compounds (I) are disclosed, e.g. 2-amino-4-(1,3-benzodioxol-5-yl)-6-benzylxy-pyridine-3,5-dicarbonitrile (Ia).



(Ia)

ADMINISTRATION

Dosage is 0.1-10000 (preferably 1-100) $\mu\text{g/kg}$ parenterally or 0.1-10 (preferably 1-4) mg/kg orally. (I) may also be administered locally.

EXAMPLE

A solution of 344 mg sodium in 20.7 ml benzyl alcohol was treated with 660 mg malonodinitrile and 750 mg piperonal, stirred for 16 hours at room temperature, neutralized and partitioned between

water and dichloromethane. The organic phase was worked up to give, after chromatographic purification, 872 mg (40.1%) of 2-amino-4-(1,3-benzodioxol-5-yl)-6-benzylxy-pyridine-3,5-dicarbonitrile (Ia).

TECHNOLOGY FOCUS

Organic Chemistry - Preparation: Three methods of preparation of (I) are claimed. Typically (a) a pyridine derivative of formula (II) is reacted with an amine of formula NHR_4R_5 (III); or (b) a benzaldehyde derivative of formula (VII) is reacted with malonodinitrile and an alcohol of formula R_6OH (VI) in presence of a base to give (I; $\text{R}_4, \text{R}_5 = \text{H}$).

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(I)



(VII)

X = leaving group.
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